IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF OHIO
WESTERN DIVISION

In re: ORTHO EVRA® PRODUCTS LIABILITY LITIGATION	)	N.D. Ohio Case No. 1:06-cv-40000
	)	
	)	MDL Docket No. 1742
This Pleading Relates to:	)	
	)	Judge David A. Katz
ALL CASES	)	
	)	
MDL Case No. 1:06-cv-40000	)	

DEFENDANTS' MOTION FOR SUMMARY JUDGMENT (FEDERAL PREEMPTION)

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Defendants Johnson & Johnson, Johnson & Johnson Pharmaceutical Research & Development, L.L.C. ("PRD"), and Ortho-McNeil Pharmaceutical, Inc. ("Ortho-McNeil") move for summary judgment under Fed. R. Civ. P. 56 on the ground that Plaintiffs' state law tort claims are preempted by the Federal Food, Drug, and Cosmetic Act ("FDCA" or "the Act"), 21 U.S.C. §§ 301 *et seq.* and its implementing regulations.

In their Master Complaint, Plaintiffs assert that: 1) an FDA-approved transdermal birth control patch, Ortho Evra®, manufactured and sold by Defendants, was defective because the warnings FDA mandated regarding certain risk issues were untimely and inadequate; 2) Defendants are liable because they failed to reject FDA's specific determinations about these risk issues, and unilaterally provide different warnings; and 3) notwithstanding the FDA's determination that the patch is safe and effective for the prevention of pregnancy when used in accordance with its approved warnings, Defendants are liable under various other tort theories for the alleged side effects of the combination hormonal contraceptive.

Plaintiffs effectively argue that the warnings determined by FDA to render Ortho Evra® "safe and effective" for marketing and distribution did – at the same time – render Ortho Evra® defective under state law, for which Defendants should respond in both compensatory and punitive damages. Plaintiffs' product liability claims conflict with FDA regulatory oversight, and are preempted. Plaintiffs' "fraud on the FDA" and deceptive advertising claims are similarly preempted by the FDA's exclusive authority to determine both the information it needs to carry out its Congressional mandate as well as the remedy under the FDCA any time it determines that approval was obtained by misrepresentation, and the specificity of FDA regulations governing prescription drug advertising.

Because the conflicts created by Plaintiffs' state law claims require preemption under the Supremacy Clause of the United States Constitution and United States Supreme Court authority,

Defendants respectfully request that the Court grant summary judgment in their favor. In support of its Motion, Defendants file contemporaneously, and incorporate herein by reference: 1) a Memorandum in Support of Motion for Summary Judgment; 2) a separate volume of Exhibits; and 3) an Appendix of Authorities.

Respectfully submitted,

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MEMORANDUM IN SUPPORT

I. INTRODUCTION AND SUMMARY OF THE ARGUMENT

This Multi-District Litigation arises out of Plaintiffs' claims, in effect, that the United States Food & Drug Administration ("FDA") was "wrong" when it concluded that the Ortho Evra® birth control patch is safe and effective when used according to its labeling, and that its labeling (both initially and post-approval) meets federal standards. FDA has consistently assessed, weighed and made expert scientific determinations about the very risks that, according to Plaintiffs, make the patch defective or that should have been warned about sooner. Plaintiffs' state law claims are therefore preempted.

Federal preemption principles recognize that allowing state court juries to conclude that a drug is unreasonably unsafe due to alleged inadequacies in the labeling for a risk that FDA has considered, conflicts with the federal law that vests exclusive jurisdiction in FDA to weigh a prescription drug's benefits and risks and determine the labeling required to render a drug "safe and effective." The question is not whether FDA's expert risk-utility and labeling judgments were right or wrong, timely or slow; the question is whether allowing state courts and juries to reach *different* conclusions would stand as an obstacle to FDA's implementation of Congress' objectives. As five of FDA's former chief counsel reported to Congress in 2004:

> If every state judge and jury could fashion their own labeling requirements for drugs and medical devices, there would be regulatory chaos for these two industries that are so vital to the public health, and FDA's ability to advance the public health by allocating scarce space in product labeling to the most important information would be seriously eroded.

150 Cong. Rec. S8657, 2004 WL 1639046 (daily ed. July 22, 2004), at 2 (Apx. Tab 5).

For similar reasons, state law "fraud on the FDA" and deceptive advertising claims are preempted. Such claims "inevitably conflict with FDA's responsibility to police fraud consistently with the Administration's judgment and objectives" (*Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001)), and conflict with FDCA and FDA regulations providing specific, comprehensive requirements for prescription drug advertising (*Pennsylvania Employees Benefit Trust Fund v. Zeneca, Inc.*, 499 F.3d 239, 253 (3rd Cir. 2007), *cert. pet. pending*, U.S. No. 07-822).

II. GLOSSARY OF PARTIES AND FREQUENTLY USED TERMS

A. Parties.

Defendants Ortho-McNeil Pharmaceutical, Inc. ("Ortho-McNeil"), and Johnson & Johnson Pharmaceutical Research and Development LLC ("PRD") designed, manufactured, distributed, marketed, and sold the prescription drug Ortho Evra®; they are both wholly-owned subsidiaries of Defendant Johnson & Johnson. When used herein, "PRD" refers to both Johnson & Johnson Pharmaceutical Research and Development LLC and its predecessor, the R.W. Johnson Pharmaceutical Research Institute.

Unless otherwise indicated, the individual plaintiffs in this Multi-District Litigation are collectively referred to as "Plaintiffs" and their claims are those set forth in the Master Complaint, R. 109.

B. Terms.

The following abbreviations are frequently used in the regulatory record (excerpts of which appear as Exhs. A-MM, filed separately) and this supporting memorandum:

AUC – "area under the curve" (a pharmacokinetic term);

EE – "ethinyl estradiol" (estrogen used in Ortho Evra® patch and birth control pills);

FPL – "Final Printed Label" (labeling required for FDA approval);

INDA – "Investigational New Drug Application" (the predicate for obtaining FDA approval to conduct clinical testing with an investigational new drug);

NDA – "New Drug Application" (the predicate for obtaining FDA approval of a new drug);

NGMN – "norelgestromin" (a progestin used in the Ortho Evra® patch and a metabolite of norgestimate);

OC – "oral contraceptive" or birth control pill;

PE – "pulmonary embolism" (blood clot in the lung);

PK – "pharmacokinetics" (the science of how the body absorbs, distributes, metabolizes, and eliminates drugs);

VTE – "venous thromboembolism" (venous blood clot).

III. A BRIEF SUMMARY OF HORMONAL CONTRACEPTION AND THE ORTHO EVRA® PATCH.

The availability of a range of birth control options – ranging from barrier methods (for example, condoms and diaphragms), to intrauterine contraceptive devices, hormonal contraceptives, sterilization, and abstinence – is an important public health issue, not just a convenience, for millions of women, because (i) of the very high rate of "unintended pregnancy" in the United States and (ii) the significant and serious morbidity and mortality women encounter when they become pregnant. As explained by David Grimes, M.D.:

> Despite a range of birth control options, nearly half of the 6.4 million pregnancies each year in the United States are unintended, meaning that at the time of the pregnancy, a woman either did not want to have any more children or wanted additional children but at a later time. Avoiding unintended pregnancy is a challenge for many women throughout their lives. Nearly half (48%) of women aged 15 to 44 have experienced an unintended pregnancy, and nearly a third (31%) have experienced an unintended birth. Nearly a third (30%) of women aged 15 to 44 in the United States have experienced one or more induced abortions. Four in ten (42%) unintended pregnancies result in an induced abortion.

(Affidavit of David A. Grimes, M.D., Exh. A, ¶ 2.)

The "primary cause" of these unintended pregnancies is "[b]irth control failure," and most contraceptive failures "are due to inconsistent or incorrect use." (*Id.*, ¶ 3.) Birth control options that are both effective (when used properly) and that increase user compliance are therefore key to promoting public health. (*Id.*, ¶ 4) The birth control patch "was developed as an alternative method of delivering contraceptive steroids in an effort to increase user compliance by avoiding the daily pill-taking of combination oral contraceptives." (*Id.*)

Hormonal birth control is effective, and while it has risks, "all available hormonal birth control methods have a favorable risk-benefit profile since the risks associated with pregnancy are far greater than using hormonal birth control for all but older women who smoke cigarettes." (*Id.*, ¶ 6.) Increased risks of blood clots, for example, accompany pregnancy as well as the use of hormonal contraceptives. In fact, "the morbidity and mortality risk encountered by women who become pregnant is far greater than that associated with the use of hormonal birth control." (*Id.*, ¶ 8.) For hormonal birth control, "[o]n a public health basis, the attributable risk of morbidity or mortality from venous thromboembolism associated with hormonal contraception use by young women is small. Several times a rare event, such as venous thromboembolism, is still a rare event." (*Id.*) In short:

> There is no perfect contraceptive method for all couples who desire safe and effective birth control. Reducing the millions of unintended pregnancies in the United States which occur every year has appropriately prompted the development of alternative methods for delivering combination hormones. The FDA has determined Ortho Evra® to be a safe and effective contraceptive for prescription use in women, a decision with which I concur.

(*Id.*, ¶ 12.)

Ortho Evra® is the first and only transdermal birth control patch approved by FDA for delivering combination hormones.[1] The transdermal – or through the skin – weekly birth control patch prevents pregnancy by delivering continuous levels of a progestin (norelgestromin (NGMN)) and an estrogen (ethinyl estradiol (EE)) through the skin and into the bloodstream over a period of seven days. But instead of taking a pill each day, users of the patch apply one patch per week for three consecutive weeks each month, followed by a seven-day patch-free interval.

The transdermal delivery system used for Ortho Evra® has several benefits: a continuous steady state release of medication (as compared to the peak and trough or "saw-tooth" release levels of oral drugs); an alternative delivery method for patients who have difficulty swallowing pills or getting injections; the convenience of not having to remember to take medication at a certain time, which reduces the risk of taking the medication less frequently; and the potential for improved compliance, reducing the risk of an unplanned pregnancy and pregnancy risks.

The combination hormones in the Ortho Evra® patch have been approved as a safe and effective means of contraception for several decades. Even so, before FDA approval on November 20, 2001, Ortho Evra® was tested over a four-year period of time in clinical trials using more than 70,000 patches on more than 3,300 women. Ortho Evra® became available for use by prescription only in the United States on April 30, 2002, and remains available today as a prescription birth control alternative for women.

[1] Contraceptives that contain both an estrogen and progestin are called "combination hormonal contraceptives."

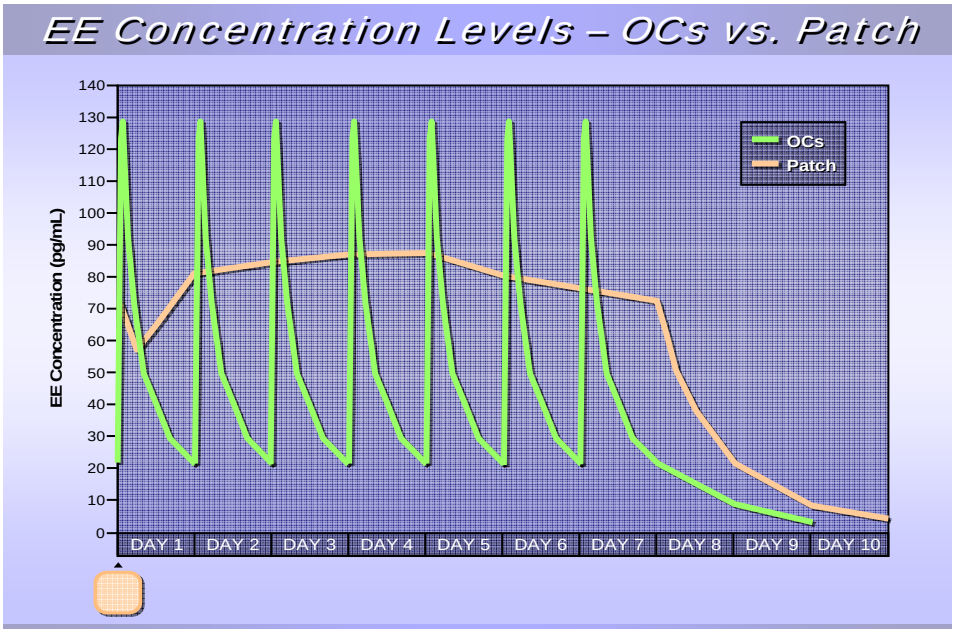
IV. PLAINTIFFS' CLAIMS

Plaintiffs' Master Complaint asserts numerous, overlapping state law tort claims based on a common thread – their claim that the Ortho Evra® patch creates a higher risk of blood clots than the risk associated with the use of birth control pills containing 20-35 micrograms (mcg) of estrogen, and the product labeling failed to adequately or timely warn consumers of that allegedly heightened risk. (Master Compl., ¶¶ 32-35, 45, 54, 69-70, 90(d), 103(f)(g), 112-127.)

Plaintiffs do not (and cannot) claim that the risk of blood clots associated with hormonal birth control generally renders the patch or its labeling defective or unreasonably dangerous. That risk has been known and regulated for many years. *See, e.g.*, 35 Fed. Reg. 9002, § 130.15 (June 11, 1970) (Apx. Tab 7); 41 Fed. Reg. 53633-53642 (Dec. 7, 1976) (Apx. Tab 9). Nor do Plaintiffs allege an adverse event unique to patch users versus birth control pill takers. Rather, Plaintiffs claim that the transdermal delivery system for estrogen *increases* the blood clot risk historically associated with hormonal contraception (*e.g.*, Master Compl., ¶ 32-35).

Plaintiffs' "increased risk" claim is two-pronged. First, Plaintiffs rely on the different pharmacokinetic (PK)[2] profiles of transdermal and oral delivery systems for combination hormones. Although "peak" estrogen concentrations (called "CMax") are approximately 25% *lower* in women using Ortho Evra® as compared to birth control pill takers, the overall estrogen exposure (the sum of the "area under curve" (AUC) in the diagram below) may be 60% *higher* for Ortho Evra® users. This is because the patch has a transdermal "steady state" hormone delivery system, while the birth control pill has a peak and trough or "saw-tooth" delivery system. *E.g.*:

[2] *See* Glossary, *supra*, p. 3.



By improperly focusing only on the AUC and ignoring the Cmax, Plaintiffs contend (incorrectly) that the PK profile for the estrogen exposure with Ortho Evra® can be used to calculate an "equivalent" oral estrogen "dose," had a pill been taken instead. To Plaintiffs' way of thinking, that means that Ortho Evra® is equivalent to a birth control pill containing a dose of 56 mcg of estrogen – they simply multiply the estrogen content of a 35 mcg birth control pill by 60% (35 mcg x 60% = 56 mcg). Such a calculation is not sound or valid science, and more importantly for the issue presented by this motion, has not been adopted by FDA.

Second, Plaintiffs extrapolate from this alleged increased estrogen "exposure" illustrated by the differing PK profiles between oral and transdermal products to the conclusion that women using the patch have a greater risk of blood clots than women taking a birth control pill with 35 mcg of estrogen. Plaintiffs assert that because at the time they used the product, the labeling for Ortho Evra® did not quantify the PK profile until November 10, 2005, or ever include a warning that the 60%/25% PK data could mean that a user was exposed to an increased risk of developing blood clots, Defendants are liable in tort to users of the patch who developed blood clots.

Counts IX and XI allege that Defendants "recklessly failed to advise the FDA" of the side effects of Ortho Evra®, and intentionally or negligently misrepresented the safety of Ortho Evra® to Plaintiffs, their healthcare providers, and the public in general ("fraud-on-the-agency" claims), and Counts XIII and XIV make similar assertions regarding Defendants' marketing and advertising materials. (Master Compl., ¶¶ 168, 170-182, 207-227.) All of Plaintiffs' state law claims turn on a factual allegation that Defendants intentionally or negligently suppressed data from the Plaintiffs, their physicians, the FDA, and the public. (*See generally* Master Compl.)

V. UNDISPUTED FACTS

In summary judgment proceedings:

> … the substantive law will identify which facts are material. Only disputes over facts that might affect the outcome of the suit under the governing law will properly preclude the entry of summary judgment.

Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 248 (1986). For a preemption analysis, the material facts are to be found in the statutes, regulations, and agency filings making up the regulatory record. *Southwestern Bell Wireless, Inc. v. Johnson County Bd. of County Comm'rs*, 199 F.3d 1185, 1194 (10th Cir. 1999).

The federal law that governs the risks asserted in Plaintiffs' Master Complaint is the Federal Food, Drug and Cosmetic Act (FDCA), 52 Stat. 1040, as amended by the Drug Amendments of 1962, 76 Stat. 780, 21 U.S.C. § 301 *et seq*. The FDCA vests exclusive jurisdiction in FDA to make the expert scientific determination that: 1) a prescription drug is safe and effective; 2) "under the conditions stated in the labeling." 21 C.F.R. § 314.50(d)(5)(viii) (Apx. Tab 6 at 21). The facts material to this motion are therefore those establishing that the risk at the core of Plaintiffs' Master Complaint was considered by FDA and the appropriate labeling regarding that risk was determined by FDA.

Plaintiffs allege, for example, that Defendants should have included a warning before November 2005 that PK profiles for the patch show estrogen exposure (AUC) that is 60% higher than the PK profile for oral contraceptives. That very data, however, was presented to FDA as early as 2004, and FDA concluded that the data required ***"no change in product labeling related to the safety"*** of the Ortho Evra® patch at that time. (Exh. B, Cover Letter (7/20/04) and Memorandum of Meeting Minutes (6/29/04), at 7 (emphasis added).) Plaintiffs' claim that the pre-2005 labeling was inadequate, rendering the patch unreasonably unsafe, is therefore in conflict with the scientific judgment of FDA.

Equally flawed is Plaintiffs' allegation that the labeling for Ortho Evra® is defective because it does not warn of increased risks of venous thromboembolisms (VTE or venous blood clots) from greater estrogen exposure. The possibility of increased blood clot risks from the transdermal delivery system for combination hormones has been considered and assessed by FDA from 1999 to the present day. *See, e.g.*, PRD's September 3, 1999 letter to FDA reporting "safety concerns" regarding "a possible increase" in the expected number of thromboembolic events in clinical investigations. (Exh. C.) That possibility has been subjected to pre- and post-approval monitoring and explored in three epidemiological studies comparing the incident of VTE in users of the patch vis-à-vis users of birth control pills. Yet *to date*, the FDA mandated labeling states that "[*i*]*t is not known* whether there are changes in the risk of serious adverse events based on the differences in pharmacokinetic profiles" and "[i]ncreased estrogen exposure [based on the differing PK profiles] *may* increase the risk of adverse events, including venous thromboembolism." (Exh. LL, Approved Label Revision (1/18/08), at 13, emphasis added.) Plaintiffs' allegations that Ortho Evra®'s labeling is inadequate because it does not warn of

increased risks of VTE therefore conflict with FDA judgments and the agency's exclusive authority and responsibility to make those judgments.

A. Historic FDA Regulation of Combination Hormonal Contraceptives.

The risks of blood clots associated with the use of hormonal contraceptives and combination hormonal contraceptives have long been a subject of FDA regulation. In 1970, for example, FDA published a Final Rule in which it required "uniform labeling" for hormonal contraceptives, stressing that the "most important complication" to be communicated to the patient "is abnormal blood clotting which can have a fatal outcome." *See* 21 C.F.R. Part 130, published at 35 Fed. Reg. 9001 (June 11, 1970), at 9002 (Apx. Tab 7). The regulation further required manufacturers to include inserts to be dispensed with the oral contraceptive, that included the warning:

> The oral contraceptives are powerful and effective drugs which can cause side effects in some users and should not be used at all by some women. The most serious known side effect is abnormal blood clotting which can be fatal.

Id. at 9002-9003.

In 1976, FDA issued its "revised physician and patient labeling" for combination hormonal contraceptives, based on "[s]ignificant new information" reported regarding thromboembolic (blood clot) disorders and other risks. 41 Fed. Reg. 53633 (Dec. 7, 1976) (Apx. Tab 9). The required labeling included contraindications for any women with "[t]hrombophlebitis or thromboembolic disorders" or a "past history of deep vein thrombophlebitis or thromboembolic disorders"; a warning that the "use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, …"; a further warning that an "increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established"; and the increased risk for

thromboembolic disease or complications based on the age or other conditions of the patient. *Id*. at 53634-53640 (Apx. Tab 9). "Abnormal blood clotting" is the first explanation under "The Dangers of Oral Contraceptives" for the patient insert. *Id*. at 53640.

Thus, when Ortho-McNeil investigated its combination hormonal contraceptive, it was covering well-plowed ground – the Ortho Evra® patch simply utilized a different method of *delivering* combination hormones that have a well-recognized, reported increased risk of blood clots.

B. 1996-2000 – Investigational New Drug Application.

On May 1, 1996, Ortho-McNeil submitted an Investigational New Drug Application (INDA)[3] to FDA for Ortho Evra®. Over the next four years, PRD conducted clinical trials and consistently met with FDA to discuss the labeling needed for the first label for a *transdermal* combination hormonal contraceptive.

Both PRD and FDA paid close attention to the potential that the transdermal delivery system could affect the blood clot risks historically associated with combination hormone contraceptives. For that reason, Dr. Gary Shangold, Senior Director for Regulatory Affairs at PRD placed a call to Dr. Lisa Rarick, Division Director for the FDA, on September 3, 1999, "to inform her of a recent safety concern." (Exh. D, Record of Contact (9/3/99).) Dr. Shangold explained that he had come across a "cluster" of seven cases (five of which were in Europe) "of thrombolic events" with patch users. (*Id*.) That same day, PRD's Associate Director of Regulatory Affairs wrote Dr. Rarick to report "preliminary IND[A] Safety Report information as received from a preliminary database review" – *i.e.*, "a possible increase over the expected number of thromboembolic events observed in this relatively small group of women …." (Exh.

[3] *See* Glossary, *supra*, p. 4 and 21 C.F.R. §§ 312.3(b), 312.20 (Apx. Tab 6 at 14, 16).

C.) The letter states that once "the complete clinical information has been gathered and its statistical analysis" completed, PRD will submit its follow-up report. (*Id*.) That report, submitted March 13, 2000, provided a narrative and summary of the data collected on each case, and the conclusion that only two thromboembolic events occurred, one of which involved incorrect product use. (Exh. F, Letter from PRD to FDA (3/13/00).)

Thus, FDA was made aware of a "possible increase over the expected number of thromboembolic events" (Exh. C) as early as 1999, before a New Drug Application for the Ortho Evra® patch was ever submitted. Both the significance and statistical validity of that "possible increase" were investigated and included in FDA's labeling and approval determinations.

C. 2000-2001 – New Drug Application and FDA Approval of Initial Labeling.

Ortho-McNeil submitted its New Drug Application (NDA)[4] to FDA for Ortho Evra® on December 21, 2000. (Exh. G, Cover Letter transmitting NDA 21-180 (12/21/00).) Over the next year, representatives of PRD and FDA met and communicated on a regular basis regarding clinical testing and the appropriate labeling (Final Printed Label or FPL) for the Ortho Evra® patch. (*See, e.g.*, Exh. H, PRD Comparator Chart (11/01).)

Based on a "solid database" of safety and clinical information, and a sufficient preclinical program, Dr. Daniel Davis – the FDA medical officer assigned to the Ortho Evra® New Drug Application – recommended approval of Ortho Evra® on November 20, 2001 as a transdermal combination hormonal contraceptive for the prevention of pregnancy (Exh. I, FDA Medical Officer Review (11/6/01), at 4, 6, 14) and FDA issued an Approval Letter, stating that "adequate information has been presented to demonstrate that the drug product is safe and effective for use

[4] *See* Glossary, *supra*, p. 4, and 21 U.S.C. § 355(b), (d) (Apx. Tab 3 at 21, 27-28); 21 C.F.R. § 314.50 (Apx. Tab 6 at 17).

as recommended in the agreed upon labeling text" (Exh. E, Approval Letter and Final Printed Label (11/20/01)).

The Executive Summary of the Medical Review summarizes the basic similarity of the patch to oral contraceptives (which prompted the use of oral contraceptive labeling in the FPL), and the distinct delivery system (which required additional labeling):

> It is this reviewer's opinion that in addition to the class labeling for oral contraceptives, the FPL should also include some of the factual efficacy and safety data from the three large clinical trials …. This will help to better inform both healthcare providers and consumers about this new delivery system for combination hormonal contraception.

(Exh. I at 4 (emphasis in original).)

The "Summary of Clinical Findings" reflects FDA's expert opinion that the benefits of the transdermal contraceptive outweigh the known clotting risks, even when the precise quantifications of those risks vis-à-vis oral contraceptives remain "unknown":

> The standard warnings and precautions for combination hormonal contraceptives should be followed in the FPL, with special attention to the fact that this will be the first transdermal delivery system marketed in the world for pregnancy prevention. Therefore, the FPL needs to state that ***it is unknown*** whether EVRA™ is distinct for many of the specific parameters listed in the class label for oral contraceptives. Special information should be included concerning the ***possible*** increased risk of venous thromboembolism (VTE or DVT) with this combination hormonal contraceptive.

(*Id*. at 8 (emphasis added).) Such conclusions are classic examples of FDA's scientific risk/benefit analysis in determining that a drug is safe and effective when used according to approved labeling.

In her November 20, 2001 memorandum documenting her "concurrence" to grant marketing approval, the Director of FDA's Office of Drug Evaluation III (Florence Houn, M.D., M.P.H., F.A.C.P.) reiterated the "careful consideration" FDA had given to the risks presented by

all combination hormonal contraceptives, and her conclusion, weighing same, that the approved labeling warranted marketing approval:

> This memo documents my concurrence with the … grant [of] marketing approval for ORTHO EVRA, a combination hormonal transdermal contraceptive indicated for preventing pregnancy. … Careful consideration was given to the two cases of venous thromboembolic events. This product increases the risk of venous thromboembolic events, as do other combined hormonal forms of contraception, and this fact is included in the labeling.

(Exh. J, FDA Memorandum (11/20/01).) Because those risks are reflected in the warning section of the FPL (Exh. E at 14), the approval letter issued by FDA states that Ortho Evra®'s FPL "must be identical" to the approved labeling text – otherwise, the product could be rendered "misbranded" and "unapproved." (*Id*. at 1.)

D. FDA's Approved Labeling Addressed the Same Pharmacologic Issues at the Core of Plaintiffs' Complaint.

The issues at the core of Plaintiffs' claims – the different PK profiles of a transdermal and oral delivery system for hormonal contraceptives and the potential link between higher estrogen exposure and increased blood clot risk – were the very same issues at the core of FDA's risk-benefit analysis and labeling decisions at the time Ortho Evra® was approved. They were reviewed, assessed, and – when FDA determined it was appropriate to do so – included in the approved labeling.

First, the FPL contained extensive information on blood clot risks from the use of combination hormonal contraceptives generally:[5]

[5] FDA required "a combination of the old class labeling for OCs, the June 1999 *draft* guidance for OC class labeling, [and] the recent NuvaRing™ label" (Exh. I at 51). NuvaRing™ was the "first transvaginal delivery system for hormonal contraception." (*Id*.)

CONTRAINDICATIONS

ORTHO EVRA™ should not be used in women who currently have the following conditions:

- Thrombophlebitis, thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Cerebro-vascular or coronary artery disease (current or past history)
- Valvular heart disease with complications (103)
- Severe hypertension (103)
- Diabetes with vascular involvement(103)
- Headaches with focal neurological symptoms
- Major surgery with prolonged immobilization
- Known or suspected carcinoma of the breast or personal history of breast cancer
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use
- Acute or chronic hepatocellular disease with abnormal liver function (103)
- Hepatic adenomas or carcinomas
- Known or suspected pregnancy
- Hypersensitivity to any component of this product

WARNINGS

* * *

The use of combination hormonal contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

* * *

a. Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of hormonal contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease (2,3,19-24). Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization (25). The risk of thromboembolic disease associated with hormonal contraceptives is not related to length of use and disappears after hormonal contraceptive use is stopped (2). A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of hormonal contraceptives (9,26). The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions (9,26). If feasible, hormonal contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, hormonal contraceptives should be started no earlier than four weeks after delivery in women who elect not to breast-feed.

* * *

b. Myocardial Infarction

An increased risk of myocardial infarction has been attributed to hormonal contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current hormonal contraceptive users has been estimated to be two to six (4-10) compared to non-users. The risk is very low under the age of 30.

* * *

c. Cerebrovascular diseases

Hormonal contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, and smoking interacted to increase the risk of stroke (27-29).

(Exh. E at 12-15.)

Second, FDA required additional labeling to address the "unknowns" accompanying the world's first transdermal delivery system for combination hormones. Immediately under the "black box" warning for smokers, FDA added:

> There is no epidemiologic data available to determine whether safety and efficacy with the transdermal route of administration would be different than the oral route.

(Exh. H at 16, Exh. E at 13.) Immediately after the OC warning on thromboembolism (*see supra*, p. 16), FDA added information on the two adverse events reported by PRD in 1999:

> In the large clinical trials … one case of non-fatal pulmonary embolism occurred during Ortho Evra™ use, and one case of post-operative non-fatal pulmonary embolism was reported following Ortho Evra™ use. It is unknown if the risk of venous thromboembolism with Ortho Evra™ use is different than with use of combination oral contraceptives.

(Exh. H at 18; Exh. E at 14.) And immediately after the OC warning on the "persistence of vascular disease" in users of combination hormones between the ages of 40-49, FDA highlighted the "unknown" distinction between OCs and the patch with regard to blood clots, by adding:

> It is unknown whether ORTHO EVRA® is distinct from combination hormonal contraceptives with regard to the occurrence of venous and arterial thrombosis.

(Exh. H at 21; Exh. E at 16.)

Third, as part of its November 2001 approval of the Ortho Evra® New Drug Application, the FDA required post-marketing surveillance for DVT and PE events involving users of the patch. (Exh. I at 52.)

E. Post-Approval Pharmacokinetic Studies Lead to Label Revisions in 2005.

On June 29, 2004, FDA and PRD held a "Guidance" meeting to discuss recent PK data from clinical studies conducted by PRD on four post-approval commercial lots of ORTHO EVRA®. (Exh. B.) At that meeting, FDA indicated that the data provided by PRD suggested that the tested lots "are producing serum ethinyl estradiol [EE] concentrations that are ***more than 60% higher***" (based on AUC and average concentration values) than those produced by the oral

contraceptive to which it had originally been compared in the 2000 study. (*Id*. at 6-7, emphasis added.)

Based on its analysis of the provided data, FDA recommended: 1) a "more thorough investigation" of release rates in pre- and post-approval patch lots; 2) that a "figure" showing a 20 mcg EE release rate for Ortho Evra® be removed (*id*. at 7);[6] and 3) that the "Description" and "Dosage and Administration" sections of the labeling be revised "to clarify the amount of [EE] delivered by ORTHO EVRA relative to oral contraceptive products that contain [EE]." (*Id*. at 1.)[7] But *no* revision in the labeling relating to the safety of Ortho Evra® was warranted by the "60% higher" AUC values:

> [B]ased on safety data presented at the meeting and your meeting package, no change in product labeling related to the safety of ORTHO EVRA is needed at this time.

(*Id*. at 7.)

PRD submitted the requested clarification as a proposed revision (Exh. L, Letter from PRD to FDA (11/3/04)), but continued broader discussions with FDA on the best way to encapsulate PK data and release rates in language helpful to prescribing physicians. *See, e.g.*, Exh. M, Record of Contact (1/5/05); Exh. N, Record of Contact (4/05); and Exh. O, Record of

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[6] FDA later clarified that the "figure" was a picture in the electronic Physician's Desk Reference. *See* Exh. K, Teleconference Meeting Minutes (10/19/04), at 2-3.

[7] FDA suggested the addition of the following paragraph under Dosage and Administration:

> ORTHO EVRA® is a combination transdermal contraceptive that contains 6.00 mg norelgestromin and 0.75 mg ethinyl estradiol (EE), and releases 150 micrograms of norelgestromin and 20 micrograms of EE to the bloodstream per 24 hours. This level of transdermal release of EE results in EE steady state concentrations that are similar to those achieved by an oral contraceptive product containing 35 micrograms of EE.

(*Id*.)

Contact (5/3/05). During that period, data from an additional study conducted by PRD on 13 commercial Ortho Evra® lots led to FDA's agreement that: 1) there were no statistically significant differences in the PK parameters of pre- and post-approval patches; and 2) there was no need for further studies of pre-and post-approval lots (Exh. P, Memorandum of Meeting Minutes (3/14/05), at 2-3). Further, FDA approved the addition of the following clarification to the Pharmacokinetics and Absorption descriptions of release rates:

> This level of transdermal release of EE results in exposure to EE greater than that produced by an oral contraceptive product containing 20 micrograms of EE.

(Exh. Q, Approved Label Revision (5/6/05), at 1.)

At a meeting held August 18, 2005, FDA acknowledged that the "clinical relevance" of the different PK profiles for the pill and the patch was "unknown, " but stated its desire for PRD to figure out how to convey Ortho Evra®'s higher estrogen concentrations and AUC values to physicians "in a clear manner" and "more prominently." (Exh. R, Memorandum of Meeting Minutes (8/18/05), at 3; Exh. S, Teleconference Meeting Minutes (8/18/05), at 1.) Based on those discussions, and further discussions on August 29, 2005, PRD faxed a proposed, comprehensive addition to the PK section of the Ortho Evra® label, entitled "Transdermal versus Oral Contraceptives." (Exh. T, Proposed Label Revision (8/29/05).) The proposed revision illustrated and explained the distinct PK profiles of a patch "designed to deliver" hormonal contraceptives over a 7-day period, and OCs "designed to be administered on a daily basis":

Transdermal versus Oral Contraceptives

The ORTHO EVRA® transdermal patch was designed to deliver EE and NGMN over a seven-day period while oral contraceptives (containing NGM 250 µg / EE 35 µg) are administered on a daily basis. Figures 5 and 6 present mean pharmacokinetic (PK)

profiles for EE and NGMN following administration of an oral contraceptive (containing NGM 250 µg / EE 35 µg) compared to the 7-day transdermal ORTHO EVRA® patch (containing NGMN 6.0 mg / EE 0.75 mg) in 32 healthy female volunteers. The mean pharmacokinetic profiles are very different between the two products and caution must be exercised when making a direct comparison of these PK parameters.

Figure 5: Mean Serum Concentration-Time Profiles of NGMN Following Once-Daily Administration of an Oral Contraceptive or Application of ORTHO EVRA® for 7 days to the Buttock in Healthy Female Volunteers. [Dashed Line represents simulated profiles (by superimposition principle) for doses 2 through 6 based on the first dose of a 7-day oral regimen]

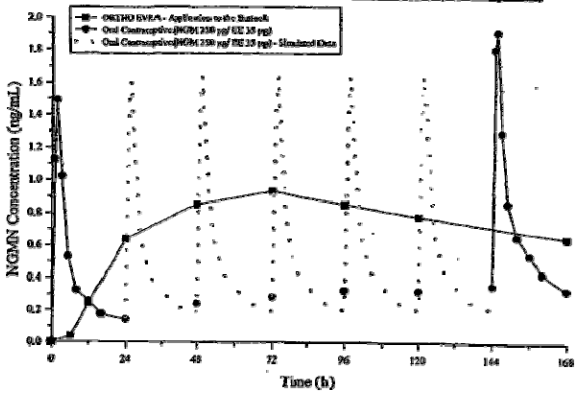

Figure 6: Mean Serum Concentration-Time Profiles of EE Following Once-Daily Administration of an Oral Contraceptive or Application of ORTHO EVRA® for 7 days to the Buttock in Healthy Female Volunteers. [Dashed Line represents simulated profiles (by superimposition principle) for doses 2 through 6 based on the first dose of a 7-day oral regimen]

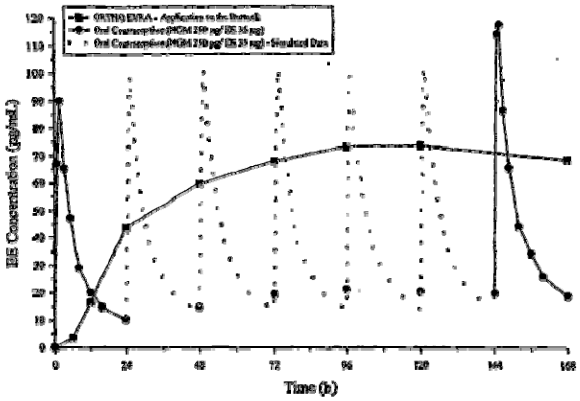

Table 2 provides the mean (%CV) for NGMN and EE PK parameters.

Table 2: Mean (%CV) NGMN and EE Steady State Pharmacokinetic Parameters Following Once-daily Administration of an Oral Contraceptive (containing NGM 250 µg / EE 35 µg) and Application of ORTHO EVRA® in Healthy Female Volunteers

Parameter	ORAL CONTRACEPTIVE[d]	ORTHO EVRA[e]
NGMN[a]		
C_{max} (ng/mL)	2.16 (25.2)	1.12 (33.6)
AUC_{24} (ng.h/mL)	17.6 (30.2)	20.8 (36.8)[b]
C_{av} (ng/mL)	0.732 (30.2)	0.888 (36.6)[c]
EE		
C_{max} (pg/mL)	133 (27.7)	97.4 (31.6)
AUC_{24} (pg.h/mL)	1183 (26.9)	1853 (33.1)[b]
C_{av} (pg/mL)	49.3 (26.9)	80.0 (33.5)[c]

[a] NGM is rapidly metabolized to NGMN following oral administration
[b] Average daily exposure, calculated as $AUC_{0-168}/7$
[c] C_{av}
[d] Cycle 2, Day 21
[e] Cycle 2, Week 3

In general, for both Cycle 1 and Cycle 2, C_{max} values for NGMN and EE were higher in subjects administered the oral contraceptive compared to ORTHO EVRA®, while overall exposure (AUC and C_{av}) was higher in subjects treated with ORTHO EVRA®. Under steady-state conditions, the C_{max} for EE was about 35% higher for the oral contraceptive, and AUC_{24} and C_{av} were approximately 55% and 60% higher, respectively, for the transdermal patch. Inter-subject variability (%CV) for the PK parameters following delivery from ORTHO EVRA® was higher relative to the variability determined from the oral contraceptive. The clinical relevance of the difference in PK profiles between transdermal and oral delivery is not known.

In Table 3, percent change in concentrations (%CV) of markers of systemic estrogenic activity (Corticosteroid Binding Globulin [CBG], Sex Hormone Binding Globulin [SHBG], and Corticosteroid Binding Globulin-Binding Capacity [CBG-BC]) from Cycle 1 Day 1 to Cycle 1 Day 22 are presented. Overall, percent change in CBG and CBG-BC concentrations were similar for ORTHO EVRA® and oral contraceptive users; percent change in SHBG concentrations were higher for ORTHO EVRA® users compared to women taking the oral contraceptive. Within each group, the absolute values for CBG, SHBG and CBG-BC were similar for Cycle 1, Day 22 and Cycle 2, Day 22.

Table 3: Mean percent Change (%CV) in CBG, SHBG and CBG-BC Concentrations Following Once-daily Administration of an Oral Contraceptive (containing NGM 250 µg / EE 35 µg) for One Cycle and Application of ORTHO EVRA® for One Cycle in Healthy Female Volunteers

Parameter	ORAL CONTRACEPTIVE (% change from Day 1 to Day 22)	ORTHO EVRA® (% change from Day 1 to Day 22)
CBG (nmol/L)	157 (33.4)	153 (40.2)
SHBG (nmol/L)	200 (43.2)	334 (39.1)
CBG-BC (nmol/L)	139 (34.8)	128 (36.3)

Despite the differences in the PK profiles of ORTHO EVRA® and an oral contraceptive (containing NGM 250 µg / EE 35 µg), estrogenic activity, as assessed by hepatic globulin synthesis, was similar when evaluating CBG and CBG-BC and higher for ORTHO EVRA® when evaluating SHBG. The clinical relevance of PK profile and pharmacodynamic (PD) response between transdermal and oral delivery is not known.

(Exh. T at 8-12.)

FDA responded that it wanted the PK profile comparisons to be moved to the Warnings section of the label. (Exh. U, Internal PRD E-mail Correspondence (10/19/05).) Following additional clarifications (Exh. V, FDA Revisions (10/19/05); Exh. W, PRD Revisions (10/25/05); Exh. X, E-mail Correspondence from PRD to FDA (10/31/05)), PRD finalized the

addition, now emboldened, to the "Warning" section. The November 2005 revision reported a 60% higher exposure to estrogen at steady-state concentrations in women using Ortho Evra®, as compared to women taking a 35 mcg pill:

WARNINGS

* * *

The pharmacokinetic (PK) profile for the ORTHO EVRA® patch is different from the PK profile for oral contraceptives in that it has higher steady state concentrations and lower peak concentrations. AUC and average concentration at steady state for ethinyl estradiol (EE) are approximately 60% higher in women using ORTHO EVRA® compared with women using an oral contraceptive containing EE 35 µg. In contrast, peak concentrations for EE are approximately 25% lower in women using ORTHO EVRA®. Inter-subject variability results in increased exposure to EE in some women using either ORTHO EVRA® or oral contraceptives. However, inter-subject variability in women using ORTHO EVRA® is higher. In general, increased estrogen exposure may increase the risk of adverse events. However, it is not known whether there are changes in the risk of serious adverse events based on the differences in pharmacokinetic profiles of EE in women using ORTHO EVRA® compared with women using oral contraceptives containing 35 µg of EE. (See CLINICAL PHARMACOLOGY, Transdermal versus Oral Contraceptives).

(*See* Exh. Y Approved Label Revision (11/10/05).)

Notably, FDA required no change in the last two sentences of the paragraph, which were part of the FPL approved in 2001. (Exh. E at 13.) Those two sentences continue yet today to state that in general, "[i]ncreased estrogen exposure *may* increase the risk" of adverse events (emphasis added), and "[i]t is not known" if there are differences in risks based on the different PK profiles of the patch and OCs. (Exh. LL at 13.)[8]

[8] FDA's insistence in placing PK data in an emboldened warning, while acknowledging that its clinical significance was "not known," was the source of some consternation within the medical community of prescribing physicians. For the prescribing physician's perspective on the use of PK data in the warning section of drug labels, *see* L.P. Schulman, et al., "Surrogate markers, emboldened and boxed warnings, and an expanding culture of misinformation: Evidence-based clinical science should guide FDA decision-making about product labeling," *Contraception* 73 (2006), at 440-442 (Apx. Tab 27). The 13 authors of that article criticize FDA's decision to place estrogen exposure results from PK studies of the Ortho Evra® patch as an emboldened "Warning" in patch labeling, because "when laboratory-based studies alone are used to explain clinical outcomes, prediction of clinical outcomes can be corrupted by a lack of clinical information …." (*Id*. at 440.)

F. Post-Approval Epidemiological Studies Lead to Label Revisions in 2006 and 2008.

FDA requested additional PK studies because women with consistently higher estrogen concentrations "*may* be at an increased risk for thrombolic and thromboembolic adverse events." (Exh. P at 3, emphasis added.) PK studies, however, cannot determine whether women exposed to higher estrogen concentrations *are* at an increased risk for blood clots. The latter analysis requires "adequately powered" epidemiological studies – i.e., studies based on analyses of data from a large number of patch users over time. *See*, *e.g.*, *id.* at 3-4, where FDA comments that the relatively small number of patch users in two European epidemiological studies prevented "meaningful safety conclusions."

At a March, 2005 meeting with PRD, FDA approved the company's initiation of two U.S. epidemiological studies. (*Id*.) The concurrent studies would involve patient populations that "do not overlap," in order "to obtain the most robust data with adequate power, in the most time-efficient fashion …." (Exh. Z, FDA Briefing Book (6/21/05), at 7, 9.) These two studies – the Boston Collaborative Drug Surveillance Program (the "Boston Study") and i3 Drug Safety (the "i3 Study") – explored the risks of arterial and venous thromboembolic events among women using Ortho Evra® compared with women using oral contraceptives with NGM and 35 mcg of EE. (*Id*.; *see also* Exh. R at 2-3.)[9]

On September 28, 2005, PRD forwarded to FDA the final report of the Boston Study (on venous thromboembolic events), which concluded that the risk of VTE events for Ortho Evra® users was closely similar to that of oral contraceptives with 35 mcg of estrogen. (Exh. AA, Cover Letter (9/28/05) and Boston Study Final Report (9/21/05).)

[9] FDA indicated in the meeting held August 18, 2005 that it was "impressed with [PRD's] attempt to address the issues [it] had been concerned with" in commissioning and supporting the Boston and i3 Studies. (*Id*. at 2.)

Thereafter, PRD forwarded to FDA an *interim* report from the i3 Study, issued February 9, 2006, indicating a "two-fold increased risk of VTE events in current EVRA users," compared with current users of OCs. (Exh. BB, i3 Study Interim Report (2/9/06), at 6.) Because the report included information that was both new and important (albeit in an interim form), Ortho Women's Health & Urology issued a press release on February 16, 2006 regarding "first results from two separate ongoing epidemiologic studies." (Exh. CC, Press Release (2/16/06), at 1.) The press release reported that: 1) the Boston Study concluded that the risk of non-fatal VTE for users of the contraceptive patch were similar to the risk for users of oral contraceptives containing 35 mcg of EE and NGM; and 2) based on "currently available data," the i3 Study reported "an approximately two-fold increase in the risk of VTE in users of Ortho Evra® compared with the users of the oral contraceptive." (*Id*.)

When it became available six months later, PRD forwarded to FDA the "Draft Final Report" of the i3 Study. The Draft Final Report agreed with the Boston Study's conclusion that there was no statistically significant difference in the relative *arterial* blood clot risks (heart attack and stroke) for Evra® users and users of a 35 mcg oral contraceptive (NGM-OC). *See* Exh. DD, E-mail Correspondence from PRD to FDA (7/5/06) and i3 Study Final Report (6/30/06), at 9 (the relative risk was "1.0 with wide confidence intervals …"). But the Draft Final Report continued its conclusion, contrary to the results of the Boston Study, that the data showed "a two-fold increased risk of VTE events in current Evra users, compared with current NGM-OC users …." (*Id*. at 9, 29.)

PRD forwarded a proposed labeling revision reflecting the different results of the two studies on July 14, 2006; FDA sent its proposed changes on September 5, 2006. (Exh. EE, Record of Contact (9/6/06), at 1.) During a teleconference on September 6, 2006, FDA

explained that the revisions were based on its epidemiologist's conclusion that the two epidemiology studies were not "of equal weight." (*Id.* at 2.) FDA therefore wanted "descriptors added to show that one study included confirmed cases of VTE while the other did not." (*Id.*) PRD promptly forwarded its explanation as to why the two epidemiology studies "were performed with equal scientific rigor and are of equal scientific validity." (Exh. FF, Correspondence from PRD to FDA (9/8/06), at 1.)

Following further FDA consideration of the additional information, on September 20, 2006, FDA approved the following label revisions (additions underlined):

INDICATIONS AND USAGE

The pharmacokinetic profile for the ORTHO EVRA® transdermal patch is different from that of an oral contraceptive. Healthcare professionals should balance the higher estrogen exposure and the possible increased risk of venous thromboembolism with ORTHO EVRA® against the chance of pregnancy if a contraceptive pill is not taken daily. (See BOLDED WARNING; WARNINGS; CLINICAL PHARMACOLOGY, Transdermal versus Oral Contraceptives).

WARNINGS

The pharmacokinetic (PK) profile for the ORTHO EVRA® patch is different from the PK profile for oral contraceptives in that it has higher steady state concentrations and lower peak concentrations. AUC and average concentration at steady state for ethinyl estradiol (EE) are approximately 60% higher in women using ORTHO EVRA® compared with women using an oral contraceptive containing EE 35 µg. In contrast, peak concentrations for EE are approximately 25% lower in women using ORTHO EVRA®. Inter-subject variability results in increased exposure to EE in some women using either ORTHO EVRA® or oral contraceptives. However, inter-subject variability in women using ORTHO EVRA® is higher. It is not known whether there are changes in the risk of serious adverse events based on the differences in pharmacokinetic profiles of EE in women using ORTHO EVRA® compared with women using oral contraceptives containing 35 µg of EE. Increased estrogen exposure may increase the risk of adverse events, including venous thromboembolism. (See CLINICAL PHARMACOLOGY, Transdermal versus Oral Contraceptives).

The risk of venous thromboembolism (VTE) in users of ORTHO EVRA® compared to users of oral contraceptives containing norgestimate and 35 mcg of EE was assessed in two epidemiological studies with a nested case control design conducted in the U.S. in women from ages 15 to 44 years. Both studies were conducted using electronic health care claims data. One of these studies, which also included patient chart review, found an increased risk of VTEs for current users of ORTHO EVRA® compared to current users of the oral contraceptives. The odds ratio for current users in this study was 2.4 (95% CI 1.1 – 5.5). The other study did not find an increase in risk of VTEs for current users of ORTHO EVRA® (odds ratio 0.9 [95% CI 0.5 – 1.6]).

In 3 large clinical trials (N= 3,330 with 1,704 women-years of exposure), one case of non-fatal pulmonary embolism occurred during ORTHO EVRA® use, and one case of post-operative non-fatal pulmonary embolism was reported following ORTHO EVRA® use.

ORTHO EVRA® and other contraceptives that contain both an estrogen and a progestin are called combination hormonal contraceptives. As with any combination hormonal contraceptive, the clinician should be alert to the earliest manifestations of thromboembolic disorders (thrombophlebitis, VTE including pulmonary embolism, cerebrovascular disorders, and retinal thrombosis). Should any of these occur or be suspected, ORTHO EVRA® should be discontinued immediately.

Detailed Patient Labeling

OTHER CONSIDERATIONS BEFORE USING ORTHO EVRA®

Hormones from patches applied to the skin get into the blood stream and are removed from the body differently than hormones from birth control pills taken by mouth. **You will be exposed to about 60% more estrogen if you use ORTHO EVRA® than if you use a typical birth control pill containing 35 micrograms of estrogen.** In general, increased estrogen exposure may increase the risk of side effects.

The risk of venous thromboembolic disease (blood clots in the legs and/or the lungs) may be increased with ORTHO EVRA® compared with that of oral contraceptives containing norgestimate and 35mcg of estrogen. This risk has been examined in two separate studies. Both studies were conducted using information from insurance claims. One study, which in addition reviewed patient charts, found a doubling of the risk for thromboembolic disease in users of ORTHO EVRA® compared with women using these oral contraceptives, and another study found no increase in risk of thromboembolic disease for women using ORTHO EVRA®. You should discuss this possible increased risk with your healthcare provider before using ORTHO EVRA®. Call your healthcare professional immediately should any of the adverse effects listed under "WARNING SIGNALS" occur while you are using ORTHO EVRA®. (See below.)

RISKS OF USING HORMONAL CONTRACEPTIVES, INCLUDING ORTHO EVRA®

1. Risk of Developing Blood Clots

The risk of venous thromboembolic disease (blood clots in the legs and/or the lungs) may be increased with ORTHO EVRA® compared with that of oral contraceptives containing norgestimate and 35mcg of estrogen (see the earlier Section OTHER CONSIDERATIONS BEFORE USING ORTHO EVRA®). You should discuss this possible increased risk with your healthcare professional before using ORTHO EVRA®. Call your healthcare professional immediately should any of the adverse effects listed under "WARNING SIGNALS" occur while you are using ORTHO EVRA®. (See below.)

(Exh. GG, Dear Healthcare Professional Letter (9/06); Exh. HH, Approved Label Revision (9/20/06), at 8, 12-13, 45-47.)

During a Media Q&A regarding the September, 2006 label revisions, FDA discussed the results of the Boston and i3 Studies, and confirmed that Ortho Evra®'s risk/benefit profile is still

"acceptable for a highly effective hormonal contraceptive." (*See* Exh. II, Media Q&A Transcript (9/06), at 6.) FDA also clarified that the September 2006 revisions did not per se strengthen the product's warnings, but simply incorporated additional clinical information consistent with FDA policy:

> This is consistent with our policy to try to give information as soon as we know it, when we think it's reliable information and even at times when we cannot make a specific change in our recommendation. We still believe that the risk benefit profile is appropriate for this particular contraceptive and safe and effective when taken with the appropriate indications, with the labeled indication.

(*Id*. at 9-10.) FDA also confirmed that while systemic estrogen exposure (at steady state concentrations) *may be 60% higher* with patch use as compared to a 35 mcg pill, FDA "*cannot conclude that, in fact, there is a greater risk*" of thromboembolic events with patch use. (*Id.* at 13 (emphasis added).)

Following the September, 2006 label revisions, both the Boston and i3 Studies were extended to provide for additional data collection and analyses, and a new, third Boston study was commissioned by PRD. (Exh. JJ, Letter from PRD to FDA (11/20/06).) The results of those studies were reported in FDA's January 18, 2008 press release announcing agency approval of an "Update" to the Ortho Evra® label. (Exh. KK.) FDA's chief medical officer explained that the update "'is an example of FDA working in tandem with the drug manufacturer'" and that the recent test results continue to suggest that increased estrogen levels "may" increase the risks of side effects, including VTE. (*Id*.) The Update reiterates that "FDA believes that Ortho Evra is a safe and effective method of contraception when used according to the labeling …." (*Id*.)

The results of the expanded data and third study were incorporated into the "Warnings" section of the label, just below the emboldened warning, as follows:

Epidemiologic, case-control studies[107-110] were conducted in the U.S. using electronic healthcare claims data to evaluate the risk of venous thromboembolism (VTE) among women aged 15-44 who used ORTHO EVRA® compared to women who used oral contraceptives containing 30-35 mcg of ethinyl estradiol (EE) and either norgestimate (NGM) or levonorgestrel (LNG). NGM is the prodrug for norelgestromin, the progestin in ORTHO EVRA®. These studies (see Table 5) used slightly different designs and reported odds ratios ranging from 0.9 (indicating no increase in risk) to 2.4 (indicating an approximate doubling of risk). One study (i3 Ingenix) included patient chart review to confirm the VTE occurrence.

Table 5: Estimates (Odds Ratios) of Venous Thromboembolism Risk in Current Users of ORTHO EVRA® Compared to Oral Contraceptive Users

Epidemiologic Study	Comparator Product	Odds Ratio (95% C.I.)
i3 Ingenix[107]	NGM/35 mcg EE[A]	2.4 (1.1-5.5)[B]
BCDSP NGM[108,109,C]	NGM/35 mcg EE	0.9 (0.5-1.6)[108] 1.1 (0.6-2.1)[109, D]
BCDSP LNG[110]	LNG[E]/30 mcg EE	2.0 (0.9-4.1)

[A] NGM = norgestimate; EE = ethinyl estradiol
[B] Increase in risk of VTE is statistically significant.
[C] BCDSP = Boston Collaborative Drug Surveillance Program
[D] Reference 109: Separate estimate from 17 months of data on new cases not included in the previous estimate (reference 108).
[E] LNG = levonorgestrel

(Exh. LL at 13.) Once again, FDA required no change to that portion of the emboldened warning stating that "[*i*]*t is not known* whether there are changes in the risk of serious adverse events based on the differences in pharmacokinetic profiles of EE in women using ORTHO EVRA® compared with women using oral contraceptives containing 35 μg of EE" and "[i]ncreased estrogen exposure *may* increase the risk of adverse events, including venous thromboembolism. (*Id*., emphasis added.)

In sum, the regulatory history of the Ortho Evra® patch establishes that:

1. FDA considered and approved warnings and contraindications that incorporated the blood clot warnings and contraindications for combination hormones generally;

2. In conjunction with PRD, FDA considered the effect of PK studies on estrogen delivery and approved, as and when appropriate, additional explanations of the differing PK profiles of the patch and the pill – differences that have "unknown" clinical significance (Exh. R at 3-4); and

3. "[W]orking in tandem" with PRD (Exh. KK), FDA has continually considered the possibility that a patch user's 60% greater exposure to EE may increase the risks

> of blood clots, and at all relevant times (and up to the present), has mandated labeling language that increased estrogen exposure "may" increase the risk of adverse events, including VTE.

The application of the federal law of preemption to these facts entitle Defendants to judgment as a matter of law on Plaintiffs' Master Complaint.

VI. PLAINTIFFS' STATE LAW CLAIMS ARE PREEMPTED BY FDA'S CONGRESSIONAL MANDATE TO CONTROL THE RESOLUTION OF THE VERY RISK ISSUES THAT COMPRISE THE CORE OF THOSE CLAIMS.

A. Express and Implied Preemption.

Preemption doctrines have evolved in federal jurisprudence as a means of enforcing the Supremacy Clause of the United States Constitution, which establishes federal legislation as "the supreme Law of the Land" that binds the judges of every state. U.S. Const. art. VI, cl. 2. (Apx. Tab 1.) Because Congress has the power to preempt state law, divining Congress' preemptive intent in federal legislation is the "ultimate touchstone" for determining its preemptive effect; generally, it is presumed that Congress does not intend to preempt state law in areas of traditional state regulation. *Malone v. White Motor Corp.*, 435 U.S. 497, 504 (1978), *aff'd* by 444 U.S. 911 (1979) (quoting *Retail Clerks v. Schermerhorn*, 375 U.S. 96, 103 (1963)); *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485.

Preemption takes two forms. First, a federal statute may expressly preempt state law – *i.e.*, a preemptive intent may be "explicit" in the statute's language. *Jones v. Rath Packing Co.*, 430 U.S. 519, 525 (1977); *Pacific Gas & Elec. Co. v. Energy Resources Conservation & Dev. Comm'n*, 461 U.S. 190, 204 (1983). Here, Defendants do not assert that Plaintiffs' claims are expressly preempted by the FDCA.

Second, a preemptive intent may be "implicit" in the structure and purpose of the federal statute (*Jones, supra*, 430 U.S. at 525) – commonly referred to as "implied" preemption. There

are two types of implied preemption – "field" and "conflict." Field preemption occurs when a federal scheme of regulation is "sufficiently comprehensive to make reasonable the inference that Congress 'left no room for'" a claim under state law. *California Fed. S. & L. Assn. v. Guerra*, 479 U.S. 272, 281 (1987).[10] "Conflict" preemption occurs when "'it is impossible … to comply with both state and federal law," and/or the state law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 372-373 (2000) (citation omitted). "Conflict" preemption is the issue presented in this case.

Conflict preemption is determined through an analysis of both the federal statute and its implementing regulations, as informed by interpretations of the regulatory agency vested with the authority and responsibility to implement Congress' statutory objectives. *Geier v. American Honda Motor Co., Inc.*, 529 U.S. 861, 883 (2000) (when "the subject matter is technical; and the relevant history and background are complex and extensive," the agency required to carry out Congress' mandate "is likely to have a thorough understanding of its own regulation and its objectives and is 'uniquely qualified' to comprehend the likely impact of state requirements"). Here, as in *Geier*, "the subject matter" – the FDCA and its regulatory scheme – "is technical; and the relevant history and background are complex and extensive." *Id*. And here, as in *Geier*, the agency required to carry out Congress' mandate – FDA – has "a thorough understanding of its

[10] The Drug Amendments of 1962, Pub. L. No. 87-781, § 202, 76 Stat. 793, for example, state that those amendments – which expanded FDA jurisdiction to include "efficacy" (as well as safety) of prescription drugs – did not preempt the entire *field* of drug efficacy regulation. *See* 71 Fed. Reg. 3922, 3935, n.8 (Jan. 24, 2006; *eff*. June 30, 2006) ("Final Rule Preamble") (Apx. Tab 11) ("[n]othing in the amendments … shall be construed as invalidating any provision of State law … unless there is a direct and positive conflict between such amendments and such provision of State law").

own regulation and its objectives and is 'uniquely qualified' to comprehend the likely impact of state requirements."

B. "Obstacle" Conflict Preemption.

State law acts as an "obstacle to the accomplishment of the full purposes and objectives of Congress" (*Crosby*, *supra*, 530 U.S. at 373), when: 1) it conflicts with the methods utilized by a federal agency to carry out those objectives; and/or 2) it interferes with agency judgments and mandates. *Int'l Paper Co. v. Ouellette*, 479 U.S. 481, 494 (1987) ("[a] state law … is pre-empted if it interferes with the methods by which the federal statute was designed to reach [its] goal[s]"; *Perez v. Campbell*, 402 U.S. 637, 650-652 (1971) (whether conflicts exist between state and federal law depends not on the state law's purpose, but on state law effect on a federal regulatory plan); *Crosby*, 530 U.S. at 379 ("[t]he fact of a common end hardly neutralizes conflicting means …."); *Geier*, *supra* (regulation promulgated by the Department of Transportation that evinced a deliberate intent to provide choices for passive restraint devices in automobiles preempted state law claim that an automobile was "defective" because it did not have a specific type of passive restraint device (airbag)).

Thus, when analyzing "obstacle" preemption in the context of state law product liability claims, courts must determine whether allowing those claims to go forward would interfere with either the federal agency's exclusive authority to *weigh and determine* product risks, or its *method* for carrying out its Congressional mandate. *See, e.g., Geier*, *supra*.

The plaintiff in *Geier* asserted that her automobile was negligently and defectively designed, under District of Columbia tort law, because it lacked a driver's side airbag. *Geier*, 529 U.S. at 865. The manufacturer of the automobile defended on the grounds that the plaintiff's state tort claims were preempted by a Federal Motor Vehicle Safety Standard ("FMVSS") promulgated by the Department of Transportation ("DOT") under the authority of the National

Traffic and Motor Vehicle Safety Act. *Id*. at 864-865. The plaintiff argued that preemption did not bar her state law claim because the FMVSS at issue simply set a "minimum airbag standard" for autos, and "[a]s far as FMVSS 208 is concerned, the more airbags, and the sooner, the better." *Id*. at 874. However, "that was not the Secretary's view." *Id*. Rather, DOT comments accompanying the promulgation of FMVSS 208, as well as the agency's explanation in *amicus* briefs and position statements, "make clear that the standard deliberately provided the manufacturer with a range of choices among different passive restraint devices" that would "bring about a mix of different devices introduced gradually over time …." *Id.* at 875-877, 879.

In *Geier*, the *mandate* of the FMVSS standard was to provide a *range of choices* among different passive restraint devices; the *method* for providing that range was to introduce the mix "gradually over time[.]" *Id*. at 875. According deference to DOT's interpretation of the regulation's methods and objectives (as well as the deleterious effect of state law product liability claims on those methods and objectives), the *Geier* Court concluded that a rule of state tort law imposing a duty on manufacturers to install airbags rather than *any other* passive restraint system "would have presented an obstacle to the variety and mix of devices that the federal regulation sought…[and the] gradual passive restraint phase-in that the federal regulation deliberately imposed." *Id.* at 881.

In short, when a federal agency vested with the authority and responsibility to carry out Congressional objectives has: 1) instituted a method for weighing competing interests or a particular risk; 2) utilized that method to reach an unambiguous decision as to how those interests or risks should be resolved in a particular case; 3) implemented that conclusion via a specific mandate; and 4) interpreted the statutory provisions and regulations through which such determinations are made as necessarily having preemptive effect; then 5) allowing the state law

claims based on that same risk to go forward would stand as an obstacle to Congressional purposes.

FDA: 1) has instituted a complex and comprehensive method of protocols, data collection and analysis, accompanied by interactive exchanges with the manufacturer of a prescription drug, to weigh specific risks against the benefits of a drug; 2) uses those methods to make expert determinations as to whether a prescription drug is "safe and effective" when used according to approved labeling and the content of that labeling; 3) implements those determinations by mandating the use of the approved labeling; and 4) determined[11] that state law product liability claims that allow juries to reach different determinations regarding the labeling for a particular drug risk acts as an obstacle to its methods for carrying out Congressional objectives in the FDCA. For those reasons, numerous courts have applied obstacle preemption to dismiss complaints asserting state law tort claims against the manufacturers of prescription drugs regulated by FDA, when those complaints are based on allegedly inadequate labeling for risks considered by FDA. *See, e.g., O'Neal v. SmithKline Beecham Corp. d/b/a GlaxoSmithKline*, *slip op*. (1/30/08), No. CIV S-06-1063 FCD/DAD, 2008 WL 275782 (E.D. Cal. 2008) (Apx. Tab 18); *Dobbs v. Wyeth Pharmaceuticals*, __ F. Supp. 2d __, No. CIV-04-

[11] FDA's position on preemption of state product liability law is explained in numerous amicus briefs and regulatory pronouncements filed from 2000 to the present. *See, e.g.*, Brief for *Amicus Curiae* of the United States of America in Support of Petition for Writ of Certiorari, *Wyeth v. Levine*, No. 06-1249 (U.S. Dec. 21, 2007) (Apx. Tab 26) ("*Levine Amicus*") at 11 (in any case where "FDA was presented with information concerning the relevant risk, a jury's imposition of liability based on a drug's FDA-approved labeling would interfere with FDA's expert judgment," requiring preemption); Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848, 2853 (Jan. 16, 2008) (to be codified at 21 C.F.R. Parts 314, 601, and 814) (Apx. Tab 12) ("[T]his rule codifies longstanding agency policy and understanding" that state law having the effect of requiring labeling different from that approved by or in accordance with FDA standards "would conflict with federal law"); *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 Fed. Reg. 3922, 3934-3935 (Jan. 24, 2006) (Apx. Tab 11).

1762-D, 2008 WL 169021 (W.D. Okla. 2008) (Apx. Tab 14); *Tucker v. SmithKline Beecham Corp.*, No. 1:04-cv-1748-DFH-WTL, 2007 WL 2726259 (S.D. Ind. 2007) (Apx. Tab 20); *Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514 (E.D. Pa. 2006) (appeal pending); *Dusek v. Pfizer Inc.*, No. Civ.A. H-02-3559, 2004 WL 3631155 (S.D. Tex. 2004) (Apx. Tab 15); and *Needleman v. Pfizer Inc.*, No. Civ.A. 3:03-CV-3074-N, 2004 WL 1773697 (N.D. Tex. 2004) (Apx. Tab 17) (all preempting state law product liability claims based on the absence of warnings regarding adult or juvenile suicidality in labeling for various antidepressants). *Accord In re Bextra and Celebrex Marketing Sales Practices and Product Liability Litigation*, No. M: 05-1699 CRB, 2006 WL 2374742 (N.D. Cal. 2006) (Apx. Tab 16) (*Celebrex* litigation; discussed *infra*); *Sykes v. Glaxo-SmithKline*, 484 F. Supp. 2d 289 (E.D. Pa. 2007) (pediatric vaccine labeling litigation; discussed *infra*); *see also Zeneca*, 499 F.3d 239 (state law false advertising claims conflict-preempted given FDA's extensive, specific, and comprehensive role in regulating and monitoring prescription drug advertising).

C. Plaintiffs' State Law Product Liability Claims Are Preempted.

State law product liability claims are premised upon the allegation that a manufacturer has placed an unreasonably unsafe product into the stream of commerce. When that "product" is a prescription drug, however, its "safety" is inherently defined by its FDA-mandated labeling – *i.e.*, a drug is "safe and effective" when used in accordance with its FDA-approved labeling. 37 Fed. Reg. 16503, 16503-16504 (Aug. 15, 1972) (Apx. Tab 8). Because FDA is vested with the exclusive authority to make the determination that a particular prescription drug is "safe and effective" when used in accordance with approved labeling, product liability suits based upon a contrary assessment of a particular risk, or the proper labeling for that risk, pose an "obstacle" to FDA's ability to carry out its responsibilities under the FDCA, and are preempted.

Put another way, FDA labeling decisions regarding a particular risk establish both a "floor" and a "ceiling" for potential manufacturer liability relating to use of the drug. And because the very risks that form the core of Plaintiffs' allegations of product liability in this case are risks that were both known to FDA and the subject of FDA scientific judgments and labeling determinations, Plaintiffs' product liability allegations are preempted by federal law.

1. FDA is vested with exclusive authority to make expert scientific judgments that act as both a "floor" and a "ceiling" for required labeling as to a particular risk.

Congress has charged FDA with the responsibility to review every new drug to ensure that the drug is "safe and effective" when used in accordance with its labeling. 37 Fed. Reg. at 16503-16504 (Aug. 15, 1972) (Apx. Tab 8).[12] That responsibility rests with FDA alone:

> Under the scheme of the Act the ultimate determination of the safety of a drug is not a matter given to the courts, but one to be determined by the Food and Drug Administration[.]

United States v. 1,048,000 Capsules (Afrodex), 494 F.2d 1158, 1160 (5th Cir. 1974). In making that "ultimate determination of … safety" (*Afrodex*), FDA does not, and cannot, consider a prescription drug's safety and efficacy "in the abstract, divorced from its labeling." *Levine Amicus, supra*, at 10 (Apx. Tab 26), citing Final Rule Preamble, 71 Fed. Reg. at 3934 (Jan. 24, 2006) (Apx. Tab 11). That is so because under the scheme of the FDCA, a New Drug Application submitted to FDA must discuss why the drug's benefits outweigh its risks "'*under the conditions stated in the labeling.*'" *Id*. at 10, quoting 21 C.F.R. § 314.50(d)(5)(viii) (emphasis added in *Amicus*). Therefore, agency approval of labeling is necessarily predicated

[12] *See, also, O'Neal*, 2008 WL 275782 at *1-*3 (Apx. Tab 18); *Dobbs*, 2008 WL 169021 at *4-*6 (Apx. Tab 14), for a survey of the federal regulations setting out FDA responsibilities and methods for carrying out those responsibilities.

upon a determination that benefits outweigh risks under certain conditions reflected in the labeling.

FDA's exclusive responsibility to approve the *initial* labeling that renders a drug safe and effective, also applies to post-approval labeling *revisions*. *See* Final Rule Preamble, 71 Fed. Reg. at 3934 (Jan. 24, 2006) (Apx. Tab 11) ("the determination [as to] whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act.").

All labeling required to render a prescription drug safe and effective establishes a "floor" for potential liability. That is, a prescription drug that does not include the approved labeling may expose the manufacturer to liability for dispensing a "misbranded" drug, or for injuries caused by a drug with a "false and misleading" label. 71 Fed. Reg. 3922, 3934-3936 (Jan. 24, 2006) (Apx. Tab 11); 21 U.S.C. § 352(a) (Apx. Tab 3 at 16). That same labeling, however, also establishes a "ceiling" for potential manufacturer liability as to a particular risk. State laws that impose liability based on the *absence* of label language regarding a risk considered by FDA – *i.e.*, that require *more* labeling than that mandated by FDA – would "stymie the regulatory scheme established by Congress." FDA Letter Brief, *Perry v. Novartis Pharmaceuticals*, Case No. CIV. No. 05-5350 (E.D. Pa. 2006), at 10 (Apx. Tab 25). State law is therefore preempted "if it imposes liability for a company's failure to provide a warning that FDA has rejected, *or would reject*, as scientifically unsubstantiated …." (*Id*. at 2, emphasis added.)

In the past two years, FDA has, upon numerous occasions, explained the deleterious effect of state laws that do not recognize the "floor" and "ceiling" effect of FDA labeling determinations on its ability to carry out the purposes and objectives of the FDCA. In the Final Rule Preamble published in 2006, for example, FDA points out that failing to accord preemptive effect to FDA determinations would encourage "defensive labeling":

> Given the comprehensiveness of FDA regulation of drug safety, effectiveness, and labeling under the act, additional requirements for the disclosure of risk information are not necessarily more protective of patients. Instead, they can erode and disrupt the careful and truthful representation of benefits and risks that prescribers need to make appropriate judgments about drug use. Exaggeration of risk could discourage appropriate use of a beneficial drug.

71 Fed. Reg. 3922, 3935 (Jan. 24, 2006) (Apx. Tab 11). An inconsistent patchwork of state law requirements would inevitably "creat[e] pressure on manufacturers to expand labeling warnings to include speculative risks and, thus, to limit physician appreciation of potentially far more significant contraindications and side effects." *Id.*, citing 65 Fed. Reg. 81082, 81083 (Dec. 22, 2000) (Apx. Tab 10).

Further, any interpretation of FDA scientific judgments as simply a "floor" is contrary to FDA's "statutorily prescribed role as the expert" on "evaluating and regulating drugs." 71 Fed. Reg. at 3935 (Jan. 24, 2006) (Apx. Tab 11). State product liability law has no counterpart:

> State actions are not characterized by centralized expert evaluation of drug regulatory issues. Instead, they encourage, and in fact require, lay judges and juries to second-guess the assessment of benefits versus risks of a specific drug to the general public ….

Id. As opposed to FDA's central role in assuming responsibility for drug safety, lay judges and juries assess a drug's safety through the eyes of single, injured plaintiff on an *ad hoc* case-by-case basis.

2. <u>FDA assessments of the obstacles posed by state product liability law are properly accorded deference.</u>

Numerous courts have acknowledged and deferred to FDA's position on the preemptive effect of its expert determinations. *See Colacicco v. Apotex, Inc*. 432 F. Supp. 2d 514, 525 (E.D. Pa. 2006), *appeal pending*, 3rd Cir. No. 06-3107 (deferring to FDA position on conflict

preemption as expressed in *amicus* brief and Final Rule Preamble);[13] *In re Bextra, supra*, 2006 WL 2374742 (Apx. Tab 16) (deferring to FDA position in Final Rule Preamble was consistent with U.S. Supreme Court authority); *Dobbs v. Wyeth Pharmaceuticals, supra,* 2008 WL 169021 (Apx. Tab 14) (according deference to FDA based on facts presented); *Dowhal v. SmithKline Beecham Consumer Healthcare,* 32 Cal. 4th 910, 12 Cal. Rptr. 3d 262, 88 P.3d 1 (2004) (deferring to position of FDA that once it determines that no warning is necessary for a particular risk issue, state law cannot hold the manufacturer liable for following FDA's decision); *Sykes, supra*, 484 F. Supp. 2d at 317 (finding it "clear" that the FDA's preemption position is entitled to significant deference); *Conte v. Wyeth, Inc.*, No. CGC-04-437382, 2006 WL 2692469 (Cal. Sup. 2006) (Apx. Tab 13) (same).

Those courts that have declined to do so tend to be based on limited or unique facts. *In re Vioxx Prods. Liab. Litig.*, 501 F. Supp. 2d 776 (E.D. La. 2007), for example, declined to afford deference to the 2006 Final Rule Preamble, in a case where the prescription drug at issue was voluntarily withdrawn from the market by the manufacturer based on "'newly discovered risks.'"[14] 501 F. Supp. 2d at 779. Here, in contrast, the risks at the core of Plaintiffs' Master Complaint (blood clotting associated with hormonal contraceptives) have been known since the early 1970s, and the Ortho Evra® patch continues to be a product approved by the FDA as safe and effective when used in accordance with its labeling.

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[13] *Colacicco* was orally argued before the Third Circuit Court of Appeals on December 10, 2007.

[14] Under the "Changes Being Effected" (CBE) regulation – 21 C.F.R. § 314.70(c)(6)(iii) (Apx. Tab 6 at 31-32), manufacturers may distribute a revised warning regarding a newly discovered risk – like that at issue in *Vioxx* – without FDA approval, if the warning has been submitted to FDA, but not considered by FDA within 30 days. The CBE regulation *only* applies to "newly discovered risks"; it does not allow for unilateral manufacturer changes regarding known risks. *See Levine Amicus* Brief at 13-14 (Apx. Tab 26) (overexpansive interpretations of the CBE constitute "a mistaken view" that has been encouraged by state law actions).

Nor do other considerations offered by the *Vioxx* court apply. First, the *Vioxx* court expresses concerns that FDA's "current views on preemption" constitute a single position statement (the 2006 Final Rule Preamble) that deviates from prior statements. 501 F. Supp. 2d at 785. But as pointed out by a district court that recently rejected the *Vioxx* analysis, FDA's position on the preemptive effect of its scientific decisions has been expressed "not only in the 2006 Preamble but also in numerous *amicus curiae* briefs filed in litigation involving state court claims against drug manufacturers and others subject to labeling or warning regulations promulgated by the FDA." *Dobbs v. Wyeth Pharmaceuticals, supra*, __ F. Supp. 2d __, 2008 WL 169021, at *11 (cites omitted) (Apx. Tab 14). Further, in an *amicus* brief filed after the *Vioxx* decision, FDA notes that arguments alleging that FDA previously held a contrary position, rely "solely on snippets from Federal Register notices that did not squarely address, much less discuss," preemption issues. *Levine Amicus* Brief at 18, fn.* (Apx. Tab 26).[15] And finally (and most importantly), changes in an agency's interpretation of the effect of state law do not "require [a] Court to disregard the FDA's current position." *Dobbs*, *supra*, at *12 (Apx. Tab 14). To the contrary, it is expected that "'an agency's view of the preemptive effect of its regulations may change over time as the agency gains more experience with the interrelationship between its regulations and state laws.'" *Id*. at *12 (citation omitted). *Accord Colacicco v. Apotex*, *supra*, 432 F. Supp. 2d at 531-532 (citation omitted) ("An initial agency interpretation is not instantly carved in stone"); *Sykes*, 484 F. Supp. 2d at 314-315 (same).

Second, the *Vioxx* court declines to give deference to an agency interpretation that is not subject to the "notice and comment" required for rule-making. 501 F. Supp. 2d at 786. To the

[15] The U.S. Supreme Court agreed to hear the issues raised in the *Levine Amicus* Brief on January 18, 2008. *Wyeth Pharmaceuticals, Inc. v. Levine*, __ S. Ct. __, 2008 WL 161474 (U.S. Vt.) (Jan. 18, 2008).

extent that "notice and comment" is even relevant,[16] on January 16, 2008, FDA *did* provide notice and invite comment on the same preemption views that were expressed in its 2006 Final Rule Preamble and numerous *amicus* briefs:

> If finalized as proposed, this rule codifies longstanding agency policy and understanding with respect to [the CBE regulation]. To the extent that state law would require a sponsor to add information to the labeling for an approved drug … without advance FDA approval based on information or data as to risks that are similar in type or severity to those previously submitted to the FDA, or based on information or data that does not provide sufficient evidence of a causal association with the product, such a state requirement would conflict with federal law. In such a situation, it would be impossible to market a product in compliance with both federal and state law, and the state law would "stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Hines* [*v. Davidowitz*, 312 U.S. 52 (1941)] at 67.
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> * * *
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> By publication of this proposed rule, FDA invites comments from state and local officials.

Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848, 2853 (Jan. 16, 2008) (to be codified at 21 C.F.R. Parts 314, 601, and 814) (Apx. Tab 12).[17]

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[16] At least one court has concluded that "FDA's failure to comply with Executive Order 13132 regarding consultation with local officials about a possible conflict with state law does not mean this Court cannot consider the FDA's view of how certain state laws stand as an obstacle to the accomplishment of the objectives of Federal law." *In re Bextra* at *7 (Apx. Tab 16), citing *Hillsborough County v. Automated Medical Labs*., 471 U.S. 707, 718 (1984); *Fidelity Fed. Sav. and Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 158 n.13 (1982); *Geier*, *supra*, 529 U.S. at 883.

[17] The proposed rule amendment also points out that on September 27, 2007 (after *Vioxx* issued), Congress enacted additional legislation that "confirm[ed] that Congress intends FDA to carefully regulate the content of labeling for approved products." 73 Fed. Reg. at 2850 (Jan. 16, 2008) (Apx. Tab 12).

Those courts deferring to "FDA's view of how certain state laws stand as an obstacle to the accomplishment of the objectives of Federal law" (*In re Bextra* at *7 (Apx. Tab 16)) are in accord with U.S. Supreme Court and Sixth Circuit authority. *See, e.g., Geier, supra,* 529 U.S. at 883 (deferring to view of federal agency that is "'uniquely qualified' to comprehend the likely impact of state requirements"); *Gustafson v. City of Lake Angelus,* 76 F.3d 778, 786 (6th Cir. 1996) (where FAA had expressed its preemptive position "in several cases," the court "must give great deference to the views of a federal agency with regard to the scope of its authority"). This Court therefore should defer to FDA's view that its labeling judgments act as both a ceiling and a floor for potential manufacturer liability.

3. Scientific judgments made by FDA regarding appropriate labeling for PK information and blood clot risks to render the Ortho Evra® birth control patch "safe and effective" preempt Plaintiffs' state law product liability claims.

The risks that form the core of Plaintiffs' claims – the increased exposure to estrogen based on differences in the PK profiles of the Ortho Evra® patch and a 35 mcg (EE) pill and the alleged link between those different profiles and heightened blood clot risks – are the same issues and risks that FDA considered and determined whether, when, and how each should be included in the labeling for the patch.

a. Initial labeling determinations.

Plaintiffs allege that Ortho Evra® was defective at the time it received FDA approval because its initial labeling did not quantify the different PK estrogen profiles for the patch and OCs, or warn of increased risks of blood clots from use of the transdermal patch, vis-à-vis OCs. Both issues were considered and determined as part of FDA's approval of Ortho Evra®'s initial labeling.

First, FDA considered and determined that PRD provided a "solid database" of safety and clinical information, and conducted a sufficient preclinical program to support the pharmacokinetic information in the labeling. (Exh. I at 4, 6, 14.)

Second, FDA required the Ortho Evra® label to include the most recent labeling used for combination hormonal contraceptives with oral or vaginal delivery systems, including extensive warnings related to VTEs and other thrombotic conditions. *See infra*, at 15-17. FDA further mandated that the FPL include language that:

> It is unknown whether ORTHO EVRA™ is distinct from combination hormonal contraceptives with regard to the occurrence of venous and arterial thrombosis.

(Exh. H at 21; Exh. E at 16 .)

Third, as a direct result of Defendants' reporting of the two adverse events in September 1999 (Exh. C), FDA determined that "special information should be included [in the FPL] concerning the possible increased risk of venous thromboembolism (VTE) associated with this combination hormonal contraceptive …." (Exh. I at 8.)

Fourth, FDA made the scientific expert judgment that the FPL must highlight the absence of "epidemiologic data available to determine whether safety and efficacy with the transdermal route of administration would be different than the oral route." (Exh. H at 16; Exh. E at 13.) And to further develop the "unknowns," FDA required "[p]ost-marketing surveillance for DVT and PE events …, as these are potential serious adverse risks … with this new delivery system for contraception …." (Exh. I at 52.)

Balancing the known and potential risks with the benefits of preventing unintended pregnancy, FDA's Medical Officer Review concluded that "[a]pproval of EVRA™ as a transdermal combination hormonal contraceptive is recommended for prevention of pregnancy." (*Id*. at 4.)

b. Labeling revision determinations.

The regulatory record establishes that FDA made further scientific determinations regarding PK and blood clot labeling when – *and only when* – it had sufficient data to support a label revision. On June 29, 2004, for example, Defendants and FDA discussed emerging PK data indicating that post-approval Ortho Evra® lots might be producing serum estrogen steady state concentrations approximately 60% higher than those produced by the oral contraceptive Cilest. (Exh. B at 7.) But FDA determined that the Ortho Evra® product labeling relating to safety should not be revised: "[B]ased on safety data presented at the meeting and your meeting package, no change in product labeling related to the safety of Ortho Evra® is needed at this time." (*Id*.) It was not until October 2005, after considering additional data and proposed labeling developed by the company (in conjunction with FDA), that FDA determined that the higher estrogen AUC should be moved to the "Warnings" section of the Ortho Evra® label. (Exh. U.) Thereafter, pursuant to the interactive methods utilized by the agency (and appropriate for clarifying PK parameters that do not equate with clinical results),[18] a labeling revision was approved in November 2005.

Similarly, FDA made scientific determinations for label revisions relating to blood clot risks when, and only when, it had sufficient data to support a label revision. FDA determined that the two PE cases reported initially in 1999 were to be included in the FPL approved in 2001, and that the company must continue "[p]ost-marketing surveillance for DVT and PE events …." (Exh. I at 52.) When PRD's epidemiological study in the European Union proved to contain too few patch users for "meaningful safety conclusions" (Exh. P at 3-4), FDA approved the

[18] During a media session held September 20, 2006, FDA confirmed that while systemic estrogen exposure may be 60% higher with the patch according to PK profiles, it "cannot conclude that, in fact, there is a greater risk" of thromboembolic events with patch use. (Exh. II at 13.)

company's initiation of two broad U.S. epidemiological studies. (*Id*.) Preliminary and final results of the two studies commissioned by PRD – the Boston Study and the i3 Study – provided conflicting results. Those results were promptly reported to FDA by Defendants, and were discussed, and incorporated into Ortho Evra® labeling when, in the scientific judgment of FDA, such revisions were appropriate.

As of the time those revisions were announced, *and to date*, FDA has repeatedly confirmed that it has not determined that increased estrogen exposure in the transdermal delivery system "in fact" increases the risk of thromboembolic events. Exh. II at 13 (FDA statement to media that while systemic estrogen exposure with patch may be 60% higher than with pills according to PK profiles, the agency "cannot conclude that, in fact, there is a greater risk" of blood clots with patch use); Exh. LL at 13 ("It is not known" if there are changes in risks based on different PK profiles; increased estrogen exposure "may" increase the risk of adverse events, including VTE).

What Plaintiffs effectively seek here, via their state law claims, is a state court "appellate review" of FDA's affirmative regulation of estrogen risk issues and determinations as to the labeling required for those risk issues to render Ortho Evra® a "safe and effective" prescription drug product. Any state law mandate requiring labeling contrary to FDA methods and determinations both undercut FDA's obligation to ensure against "false or misleading" labeling, and removes FDA as regulator of drug labeling, replacing it with a state-by-state unfocused scheme of *ad hoc* regulation. *See* 150 Cong. Rec. S8657, 2004 WL 1639046 (daily ed. July 22, 2004), at 2 (Apx. Tab 5):[19]

[19] Letter entered in the Congressional Record from five former Chief Counsel of the FDA.

> If every state judge and jury could fashion their own labeling requirements for drugs and medical devices, there would be regulatory chaos for these two industries that are so vital to the public health, and FDA's ability to advance the public health by allocating scarce space in product labeling to the most important information would be seriously eroded.

Because Plaintiffs' state law claims stand as an obstacle to the accomplishment of the objectives of federal law, they are preempted. *Geier*, *supra*, 529 U.S. at 881.

4. <u>Courts have found preemption under nearly identical circumstances.</u>

Under facts directly analogous to the claims in this case, a federal district court for the Northern District of California held that plaintiffs' state law failure to warn claims were preempted, because they were based on "warning[s] which the FDA has considered and found to be scientifically unsubstantiated." *In re Bextra and Celebrex*, at *10 (Apx. Tab 16). The plaintiffs in that case claimed that the Defendants failed to warn that the prescription drug Celebrex (a Cox-2 inhibitor for pain relief) carried a greater risk of cardiovascular adverse events than other non-steroidal anti-inflammatory drugs ("NSAIDs"). The undisputed facts established that:

- The original Celebrex label approved by FDA did not warn about the risk information at the core of Plaintiffs' failure to warn claims (*Bextra* at *3) (Apx. Tab 16);
- Although a study completed in 2000 (the "CLASS" study) and provided to FDA allegedly revealed data showing "a tendency in Celebrex patients toward increased cardiovascular toxicity," FDA did not require the Defendants to modify the Celebrex label to include an additional cardiovascular warning (*id*.);
- In 2001, an FDA advisory panel made labeling revision determinations regarding the heightened cardiovascular risk associated with Vioxx (a similar Cox-2 inhibitor), but specifically determined that the 2000 CLASS study specific to Celebrex "showed that the overall rate of serious adverse cardiovascular events for patients taking Celebrex was no higher than in patients taking other NSAIDs" (*id*.);

- FDA required a Celebrex label revision in 2002 to reflect that the 2000 CLASS study showed "*no* difference in the rate of serious adverse cardiovascular events for Celebrex than for other NSAIDs" (*id*., emphasis supplied); and

- It was not until April 2005 that FDA issued a memorandum analyzing Cox-2 inhibitors and cardiovascular risk, and required the Defendants to include a "boxed warning" on the Celebrex label to highlight the potential increased risk of serious adverse cardiovascular events (*id*.).

In finding conflict-preemption of plaintiffs' state law failure to warn claims, the *Bextra* court underscored that FDA had analyzed and made specific determinations regarding the risk issue at the core of plaintiffs' claims:

> This is not a case where the FDA has not considered the risks of which plaintiffs claim the drug manufacturer should have warned; instead, the evidence properly before the Court establishes that FDA specifically considered whether Celebrex poses a greater risk of adverse cardiovascular events than other NSAIDs. The evidence also demonstrates that the FDA determined that the scientific evidence does not establish that it does. Plaintiffs' state law failure-to-warn-claims conflict with the FDA's determination of the proper warning and pose an obstacle to the full accomplishment of the objectives of the FDCA.

Bextra at *10 (Apx. Tab 16).

Here, FDA and Defendants repeatedly reviewed and assessed Ortho Evra®'s PK parameters, and how the estrogen AUC for those parameters compare with the estrogen AUC for OCs. Following its interactive methodology, FDA ultimately determined the timing, language, placement and prominence of additional information that might help to clarify the different PK parameters. And here, as in *Bextra*, FDA and Defendants repeatedly assessed emerging data from epidemiological studies. When justified by the data, FDA required the addition of labeling language reflecting the conflicting epidemiological findings on risks of VTE.

More recently, in *Sykes v. Glaxo-SmithKline*, 484 F. Supp. 2d 289 (E.D. Pa. 2007), the federal district court came to the same conclusion regarding a plaintiff's claim that a pediatric vaccine was inadequately labeled, because "FDA has considered and dismissed any risk associated with the use of thimerosal in vaccines or biologics[.]" *Id*. at 310.

The *Sykes* court noted that FDA had determined in 1999 that "[t]here is [n]o evidence of harm from the use of thimerosal as a vaccine preservative, other than local hypersensitivity reactions." *Id*. at 310 (citations omitted). Although FDA issued its conclusion after plaintiff's minor child received his vaccines, the *Sykes* court found it "reasonable … to conclude that FDA would have reached the same conclusion in 1996, when less information was available and fewer studies existed discussing a connection between thimerosal and neurological injury." *Id*.

Here, analogous to *Sykes*, FDA has never changed the mandated label statement that "it is not known whether there are changes in the risk of serious adverse events based on the differences in the pharmacokinetic profiles of EE in women using Ortho Evra® compared with women using oral contraceptives containing 35 mcg of EE." (Exh. LL at 13.) FDA determined:

- In 1999 that two adverse PE events did not require any action regarding ongoing clinical trials;
- In 2001 that the Ortho Evra® patch was "safe and effective" when used according to labeling that acknowledged the absence of epidemiological data and the occurrence of the two adverse events in 1999;
- In June 2004 that PK data indicating a 60% greater estrogen AUC for the patch vis-à-vis OCs did not require any revision to the safety labeling for the patch at that time; and
- *To this day*, that the Ortho Evra® patch is "safe and effective" when used in accordance with labeling that sets forth the results of epidemiological information developed post-approval by the company, in conjunction with FDA.

Here, as in *Sykes*, FDA-approved product labels constitute both the "floor" and the "ceiling"; to subject the defendants to liability "would upset the careful benefit-risk balance that FDA has

struck in approving a product for market." *Sykes*, 484 F. Supp. 2d at 312, deferring to FDA Final Rule Preamble, discussed *infra*. *Accord Tucker, supra* at *9 (Apx. Tab 20) (where FDA has taken definitive action on a risk issue, balancing competing interests, a state law tort claim challenging that action "stands in clear and undeniable conflict" requiring preemption); *Colacicco*, 432 F. Supp. 2d at 536-538 (preempting plaintiffs' state law failure to warn claims); *Dusek, supra* (Apx. Tab 15); *Needleman, supra* (Apx. Tab 17); *Price v. Cook*, Case No. 99-C-12-R (Cir. Ct. W.Va. July 9, 2007), at 18 (Apx. Tab 19) (state law failure to warn claims conflict-preempted given FDA's continued monitoring of the relevant evidence, and repeated determinations that any suicide warning prior to March, 2004 would have been false or misleading).

D. Plaintiffs' State Law "Fraud-on-the-Agency" and Deceptive Advertising Claims Are Preempted.

The same principles that require preemption of Plaintiffs' product claims apply equally to their "fraud-on-the-agency" and deceptive advertising claims.

1. *Buckman Co. v. Plaintiffs' Legal Committee* precludes fraud-on-the-agency claims.

Plaintiffs' allegation that Defendants "recklessly failed to advise the FDA" of the alleged side effects of Ortho Evra® with the intent to deceive FDA and others (Master Compl., Counts IX and XI, ¶¶ 168, 170-182, 207-227) is preempted under well-established U.S. Supreme Court law – *Buckman v. Plaintiffs' Legal Comm., supra*, 531 U.S. at 350.

The plaintiffs in *Buckman* alleged a "fraud-on-the FDA" claim against the manufacturers of orthopedic bone screw implants. At the invitation of the United States Supreme Court in 2000, FDA filed two amicus briefs urging preemption of the state law claims on the basis that allowing such claims interfered with FDA's exclusive jurisdiction to determine whether its findings were obtained by fraud. *See* Brief for United States as *Amicus Curiae*, *Buckman Co. v.*

Plaintiffs' Legal Committee, No. 98-1768 (U.S.) filed June 7, 2000 and Sept. 13, 2000 (Apx. Tabs 22, 23). The U.S. Supreme Court agreed. *Buckman*, 531 U.S. at 350.

First, the Court concluded that the traditional presumption against preemption did *not* apply, because "[p]olicing fraud against federal agencies is hardly 'a field which the States have traditionally occupied,' such as to warrant a presumption against finding federal pre-emption of a state-law cause of action." *Buckman* at 347, quoting *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947). Second, the Court concluded that FDA's *method* for approving medical devices was both "comprehensive," and "aimed at detecting, deterring and punishing false statements made during this and related approval processes." *Buckman* at 348-349. Third, FDA's "variety of enforcement options" provided it with flexibility that was "a critical component of the statutory and regulatory framework under which FDA pursues difficult (and often competing) objectives" and which would be undermined by plaintiffs' state law fraud-on-the-FDA claims. *Id*.

Finally, complying with both FDA's detailed regulatory scheme, as well as the tort law of 50 different states, would dramatically increase the burden facing applicants seeking FDA approval for medical devices – burdens not contemplated by Congress in enacting the FDCA. *Buckman* at 350. Those burdens could discourage new drug or medical device applicants wary of unpredictable civil liability, and force manufacturers who do go through the FDA regulatory process to submit a "deluge of information" as opposed to required materials only, which may later be deemed insufficient in state court. *Id*. at 350-351.

Here, as in *Buckman*, FDA approval processes for new drugs and labeling revisions are equally comprehensive, and include the same variety of enforcement options in cases of suspected fraud. *See, e.g.*, 21 C.F.R. § 10.30 (Apx. Tab 6 at 1) (provisions for citizens to report

wrongdoing and petition the FDA to take action); 18 U.S.C. § 1001 (Apx. Tab 2) (general criminal proscription on making false statements to the federal government); 21 U.S.C. §§ 333(a), (f)(1)(A) (Apx. Tab 3 at 6, 9) (FDA may respond to fraud by pursuing civil penalties and criminal prosecutions); 21 U.S.C. § 355(e) (Apx. Tab 3 at 28-29) (FDA may withdraw approval of a drug if it finds that the application contains any "untrue statement of material fact"); 21 U.S.C. § 331(jj)(3) (Apx. Tab 3 at 4) and 42 U.S.C. § 282(j)(5)(D) (Apx. Tab 4) (prohibiting the submission of false or misleading clinical trial information); 21 U.S.C. § 372 (Apx. Tab 3 at 54) (authorizing FDA to investigate violations of the Act and to pursue a wide range of sanctions for any discovered fraud); 21 U.S.C. § 334 (Apx. Tab 3 at 11) (authorizing FDA to seize a drug if it is adulterated or misbranded).

Likewise, Plaintiffs' claims turn on whether Defendants withheld information from FDA, made misrepresentations to FDA, and whether FDA would have approved or withdrawn its approval of Ortho Evra® if accurate information had been submitted. As in *Buckman*, all of Plaintiffs' claims that include any element of a "fraud on the agency" theory are preempted. *Accord Garcia v. Wyeth-Ayerst Labs*, 385 F.3d 961, 966 (6th Cir. 2004) (state tort remedies requiring proof of fraud on the FDA are precluded under *Buckman*).

2. Specific FDCA and FDA advertising regulations preempt deceptive advertising claims.

Finally, Plaintiffs allege that Defendants intentionally or negligently misrepresented the safety of Ortho Evra® in its advertising and physician-directed marketing materials. (*See generally* Compl., Counts VIII-IVX; ¶¶ 209, 227, 232.)[20] FDA has filed amicus briefs explaining

[20] These are the very same advertisements which were lauded in an editorial published in *Lancet* on April 2, 2005, which cited Johnson & Johnson's "cautious, safety-oriented advertisement" of the patch and urged other companies "to follow Johnson & Johnson's lead" in direct-to-consumer advertising campaigns. *The Lancet*, Vol. 365 (Apr. 2, 2005) (Exh. MM.)

why cases seeking to force pharmaceutical manufacturers to revise warnings,[21] or discontinue allegedly deceptive advertising,[22] are conflict-preempted. Further, as the Third Circuit Court of Appeals recently held, such claims are conflict-preempted because both the FDCA and FDA regulations provide specific requirements for prescription drug advertising, and the "high level of specificity in federal law and regulations with respect to prescription drug advertising is irreconcilable with general state laws that purport to govern all types of advertising." *Zeneca*, 499 F.3d at 252.

The *Zeneca* court[23] noted that Congress expressly gave FDA authority over prescription drug advertising, and detailed FDA's extensive and specific regulations on advertising and promotional labeling (*Id.* at 246),[24] including regulations that "require prescription drug

[21] Statement of Interest of the United States, *Bernhardt v. Pfizer, Inc.*, 00 Civ. 4042 (LMM) (S.D.N.Y. Nov. 13, 2000) (Apx. Tab 21).

[22] Statement of Interest of the United States, *In Re Paxil Litigation*, No. CV 01-07937 MRP (C.D. Cal. Sept. 5, 2002) (Apx. Tab 24) (urging preemption of state law claims seeking to enjoin manufacturer from continued use of FDA-approved advertising; plaintiffs' claims constituted a direct threat to FDA's exclusive authority over what regulated manufacturers told the public about regulated products).

[23] The panel hearing *Zeneca* included the Hon. Eugene E. Siler, Senior Circuit Judge for the United States Court of Appeals for the Sixth Circuit, sitting by designation. Judge Siler concurred in the Third Circuit decision.

[24] *E.g.*, 21 C.F.R. § 314.81(b)(3)(i) (Apx. Tab 6 at 40-41) ("[t]he applicant shall submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product."); 21 C.F.R. § 202.1(e)(3)(iii) (Apx. Tab 6 at 7) ("[t]he information relating to side effects and contraindications shall disclose each specific side effect and contraindication … contained in required, approved, or permitted labeling for the advertised drug …."); 21 U.S.C. § 352(n) (Apx. Tab 3 at 18-19) (requirements for prescription drug advertising); *see generally* 21 C.F.R. § 202.1(e)(6) (Apx. Tab 6 at 9) (comprehensive and specific requirements for advertising prescription drugs including an extensive, but non-exhaustive, 20-factor list of reasons why "[a]n advertisement for a prescription drug is false, lacking in fair balance, or otherwise misleading" and describing circumstances under which "[a]n advertisement may be false, lacking in fair balance, or otherwise misleading …."); 21 C.F.R. § 202.1(j)(3) (Apx. Tab 6 at 12) (providing that

advertisements to comport with approved labeling." *Id*., citing 21 C.F.R. § 202.1(e)(3)(iii) (Apx. Tab 6 at 7). Concluding that "FDA envisioned itself occupying an ongoing and extensive role in the supervision of prescription drug advertising" (*id*. at 249, citing 60 Fed. Reg. at 44210), the Third Circuit held that allowing Plaintiffs' state law deceptive advertising claims to proceed would "unnecessarily frustrate the FDCA's purpose and FDA regulations" – especially when FDA-approved labeling formed the basis for the allegedly misleading advertising. *Id*. at 251.

The same result follows here – the same extensive and specific regulations governing prescription drug advertising and promotional labeling apply, and FDA's role with respect to Ortho Evra® advertising and promotional labeling is no less ongoing, extensive, or specific. Because Plaintiffs' state law deceptive advertising claims stymie FDA's comprehensive scheme governing the regulation and monitoring of prescription drug advertising, those claims are conflict-preempted as a matter of law.

VII. CONCLUSION

Plaintiffs' Complaint seeks to have a jury of lay people "second-guess" expert scientific judgments that FDA is exclusively authorized to make, that FDA has made, and that constitute the means and methods through which FDA carries out its Congressional mandate to determine that prescription drugs are safe and effective when used in accordance with federally approved labeling. Because Plaintiffs' state law claims pose an obstacle to FDA's implementation of FDCA, and interfere with its method for carrying out its Congressional mandate, those claims are preempted, entitling Defendants to judgment as a matter of law.

"[d]issemination of an advertisement not in compliance with [§ 202.1 provisions] shall be deemed to be an act that causes the drug to be misbranded ….").

For all of these reasons, as more fully set forth above, Defendants respectfully request entry of an order granting its Motion for Summary Judgment.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on the 22nd day of February, 2008, a copy of the foregoing **Defendants' Motion for Summary Judgment (Federal Preemption)** was filed electronically. Notice of this filing will be sent to all parties by operation of the Court's electronic filing system. Parties may access this filing through the Court's System.

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